

### **REMARKS**

This paper is filed in response to the outstanding official action dated August 25, 2010 (hereafter, the “official action”) in the above-referenced application. This paper is timely filed as it is accompanied by a petition for extension of time and authorization to charge our credit card account in the amount of the requisite fee. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith to our Deposit Account No. 13-2855, under Order No. ANA-5955 (31203/30056).

Claims 1, 2, 4, 5, and 7-15 are pending.

By the foregoing, claim 14 has been amended to correct a typographical error. No new matter has been added. The applicants respectfully submit that the aforementioned typographical error did not render claim 14 indefinite. For example, page 7 of the action indicates that the Examiner understood the intended term. In view thereof, it is respectfully submitted that one of ordinary skill would have also understood the scope of the claim as originally presented. Notwithstanding the foregoing, the typographical error has been corrected and therefore the indefiniteness rejection of claim 14 should be withdrawn.

#### **Claim Rejections under 35 USC §103(a)**

Claims 1, 2, 4, 5, 7-13, and 15 have been rejected under 35 U.S.C. §103(a) as assertedly obvious over Saito *et al.*, *J. Cerebral Blood Flow Metabol.*, 17:857-864 (1997) (“Saito”) in view of Gray *et al.*, GB 2350297 (“Gray”) and Gelb *et al.*, *Canadian Anaesth. Soc. J.*:25(6):488-494 (Nov. 1978). Claim 14 has been rejected as assertedly obvious over the proposed combination of Saito, Gray, and Gelb in further view of Gallagher *et al.*, *Anesth. Analg.*, 86:488-492 (1998). The applicants respectfully traverse the rejections.

A claim may be found obvious “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 USC §103(a). A determination that a claimed invention is obvious under §103(a) is a legal conclusion involving the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Obviousness is determined from the vantage point of a hypothetical person having ordinary skill in the art to which the claimed subject matter pertains, who is presumed to have access to all prior art references in the field of the

invention. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Furthermore, obviousness must be determined as of the time the invention was made and in view of the state of the art that existed at that time. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir. 1988).

The Supreme Court identified a number of rationales that may be used to support a conclusion of obviousness, consistent with the framework set forth in its decision in *Graham v. John Deere. Co.* See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007). To support a rejection under §103, the Patent Office must clearly articulate facts and reasons why the claimed invention “as a whole” would have been obvious to a hypothetical person having ordinary skill in the art at least as of the claimed invention’s effective filing date. *KSR Int'l*, 550 U.S. at 418.

All pending claims recite a method of treating a patient having a tissue that is subject to an ischemic event comprising parenterally administering a sub-anesthetic amount of a formulation comprising a halogenated volatile anesthetic to a patient having a tissue that is subject to an ischemic event, wherein the sub-anesthetic amount is effective to improve the tissue’s resistance to or tolerance of the ischemic event. The applicants respectfully submit that the cited references—whether taken alone or in any proper combination—do not render the claimed invention obvious because one of ordinary skill in the art would not have had sufficient motivation to combine Saito with Gray, Gelb, and/or Gallagher so as to arrive at the claimed invention. Further, one of ordinary skill would not have had a reasonable expectation of success based on the proposed extraordinary modifications of Saito in view of Gray, Gelb, and/or Gallagher.

Saito discloses administering to cats, via inhalation, 0.75% halothane in 70% nitrous oxide and 30% oxygen, which corresponds to an amount of halothane sufficient to maintain a general anesthetic effect. Saito further suggests that the aforementioned halothane administration provided some protective effect against left middle cerebral artery occlusion-induced brain ischemia — at least relative to the administration of  $\alpha$ -chloralose (Saito did not perform a placebo control after induction of MCAO and thus the applicants maintain that, at best, Saito only demonstrates a protective effect relative to  $\alpha$ -chloralose administration).

The Office acknowledged that “Saito does not teach parenteral administration of a halogenated volatile anesthetic, with an emulsification adjuvant and an emulsifier in a sub-anesthetic amount....” See page 3 of the official action. Thus, the examiner turned to Gray, which discloses parenteral administration of an injectable halogenated anesthetic formulation,

and Gelb, which discloses administration of sub-anesthetic amounts of halothane in an attempt to arrive at the invention recited in claims 1, 2, 4, 5, 7-13, and 15.

In order to have sufficient motivation to modify Saito in view of Gray, one of ordinary skill in the art would have had to have had a reasonable expectation that the injectable formulation disclosed in Gray would produce a protective effect against the left middle cerebral artery occlusion-induced brain ischemic insult model disclosed in Saito. The applicants respectfully submit that one of ordinary skill would not have had a reasonable expectation that the protective effect described in Saito, which was achieved via inhalation administration of halothane, would also be achieved by parenterally administering a formulation comprising a halogenated volatile anesthetic (such as halothane), as claimed. In support of this statement, the applicants again respectfully submit that it is well known that one cannot presume that different routes of administration (of the same drug) achieve the same physiological effect. In this respect, Lucchinetti, *et al.*, *Int'l Anesthesia Res. Soc.*, 106(5):1346-1349 (May 2008), when discussing emulsified intravenous isoflurane in comparison to inhaled isoflurane, unequivocally states:

...the route of administration are known to profoundly affect pharmacokinetic and/or dynamic properties of a drug, to modify the ratio between therapeutic activities versus toxicity (therapeutic index), and are even capable of evoking novel biological actions.

See Lucchinetti at the first full paragraph of page 1346. In view of the above teaching in the art that there can be profound differences in pharmacodynamic properties attributable to different routes of administration (and with specific reference to a halogenated volatile anesthetic as claimed), it is respectfully submitted that one of ordinary skill would not have had a reasonable expectation of success based upon the proposed modification of the method disclosed by Saito (even if taken in further view of Gelb and/or Gallagher) in view of Gray. Therefore, the proposed modification would not be made by one having ordinary skill.

Moreover, both Saito and Gray are directed to methods of administering anesthetic doses and fail to disclose or suggest administration of sub-anesthetic doses. Indeed, Saito teaches in the Discussion section that any ischemic protective effect demonstrated therein is attributed to administration of an anesthetic amount of halothane by distinguishing between the awake and anesthetized states:

*Compared with the awake state*, volatile anesthetics, including halothane and sevoflurane, reduce brain damage in animals subjected to transient focal cerebral ischemia.

See Saito at the second full paragraph of page 862 (emphasis added). In view of this explicit teaching in Saito, one of ordinary skill in the art would not have had a reasonable expectation that the protective effect demonstrated in Saito (even if taken in further view of Gray, Gelb, and/or Gallagher) could be achieved by administration of a sub-anesthetic amount of a halogenated volatile anesthetic, as claimed. Consequently, in view of this explicit teaching, one of ordinary skill in the art would not expect any protective effect disclosed in Saito to be separable from the anesthetic dose administered therein (and no document can remedy this teaching). As a result, there is insufficient motivation to modify Saito to include a step of parenterally administering a sub-anesthetic amount of halogenated volatile anesthetic, as claimed.

Gelb does not remedy these deficiencies. Gelb discloses that administration, via inhalation, of a sub-anesthetic dose of halothane reduced the ventilatory response to hypoxemia. One of ordinary skill would have no motivation to combine Saito (even if taken in further view of Gray and/or Gallagher) with Gelb because the reduction of ventilation is undesirable in patients having a tissue subject to ischemia as claimed (and as disclosed by Saito). In this respect, Gelb explicitly states that “[t]he absence of a normal response to hypoxia increases the severity and, therefore, the danger of hypoxic episodes.” See Gelb at the second full paragraph of page 493. In view of this disclosure, the applicants respectfully submit that one of ordinary skill would not modify Saito (even if taken in further view of Gray and/or Gallagher) in view of Gelb because ischemia is well understood to result in tissue hypoxia and Gelb cautions against the danger of administering a sub-anesthetic amount of halothane in patients subject to hypoxic episodes. In this respect, the applicants respectfully submit that Gelb *teaches away* from the claimed subject matter because it teaches against administering a sub-anesthetic amount of a formulation comprising a halogenated volatile anesthetic to a patient having a tissue that is subject to an ischemic event, as claimed. In view of this teaching away from the claimed invention, it is improper to combine Saito with Gelb. See MPEP § 2141.02 VI (“A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” (quoting *W.L. Gore & Assoc., Inc., v. Garlock Inc.*, 721 F.2d 1540 (Fed. Cir. 1983))). Moreover, Gelb also teaches away from Saito in the same respect. See, for example, MPEP § 2145 X.D.2 (“It is improper to combine references where the references teach away from their combination.”). Accordingly, the proposed modification of Saito (even if taken in further view of Gray and/or Gallagher) with Gelb is impermissible as a matter of law in addition to being entirely inconsistent with the emphasis in Saito that its

protective effect is inseparable from the anesthetic dose administered therein as explained above.

Moreover, it is clear that Gelb is directed to exploring the effects of low concentrations of halothane present in *awake* patients (*see* the first paragraph of Gelb). Thus, one of ordinary skill would not be motivated to substitute a sub-anesthetic amount of a halogenated anesthetic for an anesthetic amount based on the teachings of Gelb in view of Saito's explicit distinction between anesthetic and awake states discussed above.

Consistent with the foregoing, Luchinetti (which is not available as prior art) explicitly references a study (which is also not available as prior art) demonstrating protective effects achieved in accordance with the claimed methods, noting that "[t]hese findings raise the *intriguing possibility* that the organ-protective actions elicited by halogenated ethers *may be largely separated from anesthetic effects if administered as emulsions*." *See* Lucchinetti at the first full paragraph of page 1347 (emphasis added). Thus, this passage in Luchinetti strongly corroborates that the claimed invention is "more than the predictable use of prior art elements according to their established functions." *KSR, supra*. In view of the foregoing evidence, the applicants respectfully submits that the pending claims are patentable.

Gallagher does not remedy the aforementioned deficiencies.

*Prima facie* obviousness under § 103(a) is a legal conclusion—not a fact—based on underlying facts. *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976); *In re Kumar*, 418 F.3d 1361, 1365 (Fed. Cir. 2005) ("Determination of obviousness under 35 USC § 103 is a legal conclusion based on underlying facts."). The present response identifies facts rebutting the alleged legal conclusion that the claimed invention is *prima facie* obvious. All of these facts must be evaluated along with the facts on which the legal conclusion was originally reached. Having requested reconsideration of the legal conclusion set forth in the official action, the Patent Office is obligated to address all of the evidence and base its forthcoming legal conclusion(s) on such evidence, uninfluenced by its earlier conclusions. *Rinehart*, 531 F.2d at 1052.

**CONCLUSION**

In view of the foregoing, reconsideration and withdrawal of the rejections and allowance of all pending claims.

Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, the examiner is urged to contact the undersigned attorney.

Respectfully submitted,

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